application on December 10, 1999. It is not clear if this Sequence listing was defective or, as appears more likely, simply not placed in the application. Enclosed is another Sequence Listing and amendment to the specification. Please advise if this is complete and sufficient.

The Interview

Dr. Hugh Sampson, licensee's representative Brenda Jarrell, and the undersigned, greatly appreciated the opportunity to meet with the examiner on August 15, 2000.

Double Patenting Rejections

Applicants have expressly abandoned related applications U.S.S.N. 09/248,674, 09/248,673 and 09/240,577. This should moot any double patenting rejections.

Rejections under 35 U.S.C. §112

Claims 1-11 and 13 were rejected under 35 U.S.C. §112, first paragraph, on the basis that applicants have only demonstrated reduction to practice with peanut allergens. This rejection is respectfully traversed.

As Dr. Sampson explained at the interview, the invention is not the cloning of the cDNA encoding the allergens at issue, but the mapping of the IgE binding epitopes, the IgG binding epitopes, and the epitopes involved in T cell interaction, which allows the design of modified allergens which have less or no IgE binding sites, but that are still reactive with IgG and T cells. These modified allergens can then be used to elicit an immune but safe reaction to the allergen to decrease allergic response to the native allergen.

Until the inventors demonstrated that one could delete the IgE binding sites while retaining the IgG and T cell sites, and retain immunogenicity, one could not have predicted that these sites would be sufficiently distinct for the modified allergen to be useful.

As demonstrated by the enclosed papers, the same methods for modification of the allergen are equally useful with allergens other than the peanut allergens described in the patent application. These include Ayuso, et al. "Identification and Mutational Analysis of Major Epitopes of the Shrimp Allerge Pen a 1 (tropomyosin) J. Allergy Clin. Immunol. 105, No. 1, part 2, abstract 423; Astwood, et al., "Identification and Characterization of IgE Bidning Epitopes of Patatin, a Major Food Allergen of Potato" J. Allergy Clin. Immunol. 105, No. 1, part 2, abstract 555; Helm, et al., "Mutation analysis of the IgE-binding epitopes of P34/Gly m Bd 30K" (soybean) J. Allergy Clin. Immunol. 105:378-384 (2000); Chatchatee, et al., "Identification of IgE and IgG Binding Epitopes on αs1-casein: Differences in Patients with Persistent and Transient Cow's Milk Allergy"(submitted); Chatchatee, et al., "Identification of IgE and IgG Binding Epitopes on β- and κ- casein in Cow's Milk Allergic Patients" (submitted).

As Dr. Sampson explained, others had thought it was the T cell epitopes that were critical, and then found that this was not the case. This is why he and the other applicants looked at the IgE, IgG and T cell epitopes together. Their goal was to reduce binding with IgE but to retain the protein conformation and T cell epitopes; not to create peptides, but full length proteins with the native conformation, to the extent possible. As subsequently demonstrated with a mouse anaphylaxis model, the modified allergens are efficacious in reducing anaphylaxis following a challenge that would be lethal for the native allergen.

Claim 8 has been amended to insert the definition of "immune stimulatory sequences" found in the application at page 7, lines 5-8.

All claims as pending upon entry of this amendment are attached in an Appendix to facilitate review by the examiner.

Respectfully submitted,

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Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: September 11, 2000

Patrea L. Pabst

APPENDIX: Claims as pending upon entry of the amendment

1. A method of making a modified allergen which is less reactive with IgE comprising
(a) identifying IgE binding sites in an allergen;
(b) modifying the allergen by mutating at least one amino acid in an IgE binding site or reacting the allergen with a compound blocking binding to at least one amino acid in an IgE binding site;
(c) screening for IgE binding to the modified allergen using serum or antibodies from a pooled patient population and screening for activation of T cells; and
(d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen and which activate T cells.

2. The method of claim 1 further comprising screening for binding of the modified allergen for binding to IgG and selecting the modified allergens which have decreased binding to IgE, activate T cells and bind to IgG.

3. The method of claim 1 wherein the modified allergen is mutated in the center of one or more of the IgE binding sites.

4. The method of claim 1 wherein the modified allergen is mutated by substituting a hydrophobic amino acid in the center of one or more of the IgE binding sites with a neutral or hydrophilic amino acid.

5. The method of claim 1 wherein binding of IgE to the modified allergen is blocked by reaction of a compound with at least one amino acid present in an IgE binding site.

6. The method of claim 5 wherein binding of IgE is blocked by reaction of the allergen with an antibody which blocks binding to one or more IgE sites but allows the allergen to still activate T cells.

7. The method of claim 1 wherein the modified allergen is a portion of a protein.

8. (amended) The method of claim 1 wherein the modified allergen is formulated with an adjuvant selected from the group consisting of IL 12, IL 16, IL 18, Ifn-γ or immune stimulatory oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response.

9. The method of claim 1 wherein the modified allergen is screened for initiation of a T cell helper 1 response.

10. The method of claim 1 wherein the modified allergen is made in a recombinant host selected from the group consisting of plants, animals, bacteria, yeast, fungi, and insect cells.

11. The method of claim 1 wherein the modified allergen is made in cells using site specific mutation.

12. The method of claim 1 wherein the modified allergen is made from a peanut allergen selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

13. The method of claim 1 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes.